PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

#14
AKO
11/20/02

In re Application of

Ii NORITAKA, et al.

Application No.: 09/509,677 Group Art Unit: 1617

Confirmation No.: 3130 Examiner: S. HUI

Filed: March 30, 2000

FOR: ORAL ADMINISTRATION PREPARATION

DECLARATION UNDER 37 C.F.R. 1.68

Honorable Commissioner of
Patents and Trademarks
Washington, D. C. 20231

Sir:

I, Naoto Kashiide, declare and state:

That I am a citizen of Japan, located at ARK Mori Bldg. 28F, No. 12-32, Akasaka 1-come, Minato-ku, Tokyo, Japan.

That I well understand the Japanese and English languages and that the attached English document marked by "A" is a full, true and faithful translation made by me of the relevant portion (indicatedby ① and ②) to "Sucralfate" of the Japanese Pharmacopeia and a copy thereof which is attached hereto under "B" and which was filed with U.S. Patent and Trademark Office on September 12, 2002.

I declare further that all statements made herein of my own knowledge are true and that all statements made on information

and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and like so made are punishable by fine or imprisonment, or both, under §1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: November 6, 2002 Naoto Kashiide

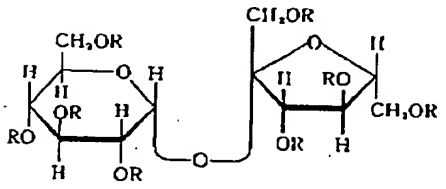
Naoto Kashiide

"A"

The portion indicated by ①:

Sucralfate

Sucrose aluminum sulfate



$C_{12}H_{30}Al_8O_{43}S_8 \cdot xAl(OH)_3 \cdot yH_2O$

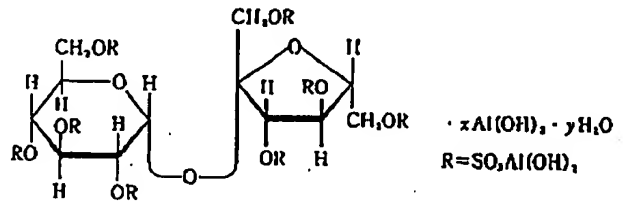
The portion indicated by ②:

Properties: This product is a white powder and it does not have a smell and a taste.

スクラルファート

Sucralfate

ショ糖硫酸エステルアルミニウム塩



$C_{12}H_{36}Al_8O_{41}S_8 \cdot xAl(OH)_3 \cdot yH_2O$

本品は定量するとき，換算した乾燥物に対し，アルミニウム（Al：26.98）17.0 ～ 21.0 %　及びショ糖オクタ硫酸エステル（$C_{12}H_{22}O_{35}S_8$：982.81）として 34.0 ～ 43.0 % を含む．

性　状　本品は白色の粉末で，におい及び味はない．

本品は水，熱湯，エタノール又はエーテルにほとんど溶けない．

本品は希塩酸又は硫酸・水酸化ナトリウム試液に溶ける．

確認試験

（1）　本品 0.05 g を小試験管にとり，金属ナトリウムの新しい切片 0.05 g を加え，注意しながら加熱融解し，直ちに水 100 mL の中に入れ，小試験管を割り，よく振り混ぜた後，ろ過する．ろ液 5 mL にニトロプルシドナトリウム試液 1 滴を加えるとき，液は赤紫色を呈する．(21)

（2）　本品 0.040 g を希硫酸 2 mL に溶かし，アントロン試液 2 mL を穏やかに加えて二層とするとき，境界面は青色を呈し，徐々に青緑色に変わる．(22)

（3）　本品 0.5 g を希塩酸 10 mL に溶かした液は，アルミニウム塩の定性反応を呈する．

純度試験

（1）　溶状　本品 1.0 g を希硫酸 10 mL に溶かすとき，液は無色澄明である．

（2）　塩化物　本品 0.5 g を希硝酸 30 mL に溶かし，沸騰するまで穏やかに加熱する．冷後，水を加えて 100 mL とし，この液 10 mL に希硝酸 3 mL 及び水を加えて 50 mL とする．これを検液とし，試験を行う．比較液には 0.01 mol/L 塩酸 0.70 mL を加える（0.50 % 以下）．(23)

（3）　重金属　本品 1.0 g をとり，塩化ナトリウム溶液（1 → 5）20 mL 及び希塩酸 1 mL を加えて溶かし，これに希酢酸 2 mL 及び水を加えて 50 mL とする．これを検液とし，試験を行う．比較液は希塩酸 1 mL を水浴上で蒸発乾固し，これに塩化ナトリウム溶液（1 → 5）20 mL，希酢酸 2 mL，鉛標準液 2.0 mL 及び水を加えて 50 mL とする（20 ppm 以下）．

（4）　ヒ素　本品 1.0 g をとり，希塩酸 5 mL に溶かし，これを検液とし，装置 B を用いる方法により，試験を行う（2 ppm 以下）．

（5）　遊離アルミニウム　本品 3.0 g に水 50 mL を加え，水浴中で 5 分間加熱し，冷後，ろ過し，残留物を水 5 mL ずつで 4 回洗い，ろ液及び洗液を合わせ，希塩酸 2 mL を加え，水浴中で 30 分間加熱する．冷後，水酸化ナトリウム試液を加えて中和し，水を加えて正確に 100 mL とし，試料溶液とする．試料溶液 50 mL を正確に量り，0.05 mol/L エチレンジアミン四酢酸二ナトリウム液 25 mL を正確に加え，pH 4.5 の酢酸・酢酸アンモニウム緩衝液 20 mL を加えた後，5 分間煮沸し，冷後，エタノール 50 mL を加え，過量のエチレンジアミン四酢酸二ナトリウムを 0.05 mol/L 酢酸亜鉛液で滴定する（指示薬：ジチゾン試液 3 mL）．ただし，滴定の終点は液の緑紫色が紫色を経て赤色に変わるときとする．同様の方法で空試験を行う（0.2 % 以下）．

0.05 mol/L エチレンジアミン四酢酸二ナトリウム液 1 mL = 1.3491 mg Al

（6）　類縁物質　定量法（2）ショ糖オクタ硫酸エステルで得られた試料溶液 50 μL につき，定量法（2）ショ糖オクタ硫酸エステルを準用し，液体クロマトグラフ法により試験を行う．試料溶液のショ糖オクタ硫酸エステルのピーク面積及びショ糖オクタ硫酸エステルのピークに対する相対保持時間が約 0.7 の類縁物質のピーク面積を自動積分法により測定し，ショ糖オクタ硫酸エステルのピーク面積に対する類縁物質のピーク面積を求めるとき，0.1 以下である．(24)

検出感度：定量法（2）ショ糖オクタ硫酸エステルで得られた標準溶液 50 μL から得たショ糖オクタ硫酸エステルのピーク高さがフルスケールの 60 ～ 100 % になるように調整する．

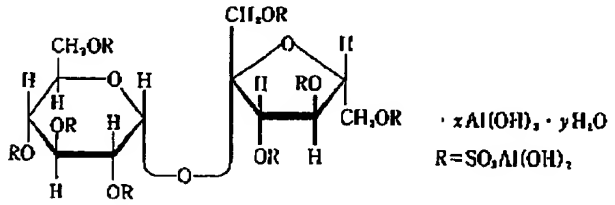
乾燥減量　14.0 % 以下（1 g，105 ℃，3 時間）．(25)

制酸力　本品を乾燥し，その約 0.25 g を精密に量り，200 mL の共栓三角フラスコに入れ，0.1 mol/L 塩酸 100 mL を正確に加え，密栓して 37 ± 2 ℃ で正確に 1 時間振り混ぜ（振とう速度毎分 150 回，振幅 20 mm）た後，5 分間水冷する．上澄液 10 mL を正確に量り，過量の酸を 0.1 mol/L 水酸化ナトリウム液で pH 3.5 になるまで滴定する．同様の方法で空試験を行う．本品 1 g につき，0.1 mol/L 塩酸の消費量は 130 mL 以上である．

スクラルファート

Sucralfate

ショ糖硫酸エステルアルミニウム塩



$C_{12}H_{30}Al_8O_{51}S_8 \cdot xAl(OH)_3 \cdot yH_2O$

本品は定量するとき，換算した乾燥物に対し，アルミニウム（Al：26.98）17.0 ～ 21.0 %　及びショ糖オクタ硫酸エステル（$C_{12}H_{22}O_{35}S_8$：982.81）として　34.0 ～ 43.0 % を含む．

性　状　本品は白色の粉末で，におい及び味はない．

本品は水，熱湯，エタノール又はエーテルにほとんど溶けない．

本品は希塩酸又は硫酸・水酸化ナトリウム試液に溶ける．

確認試験

（1）　本品 0.05 g を小試験管にとり，金属ナトリウムの新しい切片 0.05 g を加え，注意しながら加熱融解し，直ちに水 100 mL の中に入れ，小試験管を割り，よく振り混ぜた後，ろ過する．ろ液 5 mL にニトロプルシドナトリウム試液 1 滴を加えるとき，液は赤紫色を呈する．(注1)

（2）　本品 0.040 g を希硫酸 2 mL に溶かし，アントロン試液 2 mL を穏やかに加えて二層とするとき，境界面は青色を呈し，徐々に青緑色に変わる．(注2)

（3）　本品 0.5 g を希塩酸 10 mL に溶かした液は，アルミニウム塩の定性反応を呈する．

純度試験

（1）　溶状　本品 1.0 g を希硫酸 10 mL に溶かすとき，液は無色澄明である．

（2）　塩化物　本品 0.5 g を希硝酸 30 mL に溶かし，沸騰するまで穏やかに加熱する．冷後，水を加えて 100 mL とし，この液 10 mL に希硝酸 3 mL 及び水を加えて 50 mL とする．これを検液とし，試験を行う．比較液には 0.01 mol/L 塩酸 0.70 mL を加える（0.50 % 以下）．(注3)

（3）　重金属　本品 1.0 g をとり，塩化ナトリウム溶液（1 → 5）20 mL 及び希塩酸 1 mL を加えて溶かし，これに希酢酸 2 mL 及び水を加えて 50 mL とする．これを検液とし，試験を行う．比較液は希塩酸 1 mL を水浴上で蒸発乾固し，これに塩化ナトリウム溶液（1 → 5）20 mL，希酢酸 2 mL，鉛標準液 2.0 mL 及び水を加えて 50 mL とする（20 ppm 以下）．

（4）　ヒ素　本品 1.0 g をとり，希塩酸 5 mL に溶かし，これを検液とし，装置 B を用いる方法により，試験を行う（2 ppm 以下）．

（5）　遊離アルミニウム　本品 3.0 g に水 50 mL を加え，水浴中で 5 分間加熱し，冷後，ろ過し，残留物を水 5 mL ずつで 4 回洗い，ろ液及び洗液を合わせ，希塩酸 2 mL を加え，水浴中で 30 分間加熱する．冷後，水酸化ナトリウム試液を加えて中和し，水を加えて正確に 100 mL とし，試料溶液とする．試料溶液 50 mL を正確に量り，0.05 mol/L エチレンジアミン四酢酸二ナトリウム液 25 mL を正確に加え，pH 4.5 の酢酸・酢酸アンモニウム緩衝液 20 mL を加えた後，5 分間煮沸し，冷後，エタノール 50 mL を加え，過量のエチレンジアミン四酢酸二ナトリウムを 0.05 mol/L 酢酸亜鉛液で滴定する（指示薬：ジチゾン試液 3 mL）．ただし，滴定の終点は液の緑紫色が紫色を経て赤色に変わるときとする．同様の方法で空試験を行う（0.2 % 以下）．

0.05 mol/L エチレンジアミン四酢酸二ナトリウム液 1 mL = 1.3491 mg Al

（6）　類縁物質　定量法（2）ショ糖オクタ硫酸エステルで得られた試料溶液 50 μL につき，定量法（2）ショ糖オクタ硫酸エステルを準用し，液体クロマトグラフ法により試験を行う．試料溶液のショ糖オクタ硫酸エステルのピーク面積及びショ糖オクタ硫酸エステルのピークに対する相対保持時間が約 0.7 の類縁物質のピーク面積を自動積分法により測定し，ショ糖オクタ硫酸エステルのピーク面積に対する類縁物質のピーク面積を求めるとき，0.1 以下である．(注4)

検出感度：定量法（2）ショ糖オクタ硫酸エステルで得られた標準溶液 50 μL から得たショ糖オクタ硫酸エステルのピーク高さがフルスケールの 60 ～ 100 % になるように調整する．

乾燥減量　14.0 % 以下（1 g，105 ℃，3 時間）．(注5)

制 酸 力　本品を乾燥し，その約 0.25 g を精密に量り，200 mL の共栓三角フラスコに入れ，0.1 mol/L 塩酸 100 mL を正確に加え，密栓して 37 ± 2 ℃ で正確に 1 時間振り混ぜ（振とう速度毎分 150 回，振幅 20 mm）た後，5 分間水冷する．上澄液 10 mL を正確に量り，過量の酸を 0.1 mol/L 水酸化ナトリウム液で pH 3.5 になるまで滴定する．同様の方法で空試験を行う．本品 1 g につき，0.1 mol/L 塩酸の消費量は 130 mL 以上である．

Remington's Pharmaceutical Sciences

18

The dye is incorporated by trituration and geometric dilution. Powders also may be colored evenly by adding a solution of the dye in alcohol or some other volatile solvent having only a slight solvent action on the powder being colored. When this procedure is employed, the solution is added in portions, with thorough mixing after each addition, after which the solvent is allowed to evaporate from the mixture.

Many of the syrups and elixirs used as flavoring and diluting agents are colored. When such agents are used no further coloring matter is necessary. The use of colored flavoring agents is discussed in a subsequent section. However, when it is desired to add color to an otherwise colorless mixture, one of the agents described in the first section may be used.

Incompatibilities—FD&C dyes are mainly anionic (sodium salts), hence are incompatible with cationic substances. Since the concentrations of these substances are generally very low, no precipitate is evident. Polyvalent ions such as calcium, magnesium and aluminum also may form insoluble compounds with dyes. A pH change may cause the color to change. Acids may release the insoluble acid form of the dye.

Caramel

Burnt Sugar Coloring

A concentrated solution of the product obtained by heating sugar or glucose until the sweet taste is destroyed and a uniform dark brown mass results, a small amount of alkali, alkaline carbonate or a trace of mineral acid being added while heating.

Description—Thick, dark brown liquid with the characteristic odor of burnt sugar, and a pleasant, bitter taste; specific gravity not less than 1.30; 1 part dissolved in 1000 parts of water yields a clear solution having a distinct yellowish orange color which is not changed and no precipitate is formed after exposure to sunlight for 6 hr; when spread in a thin layer on a glass plate, it appears homogeneous, reddish brown and transparent.

Solubility—Miscible with water in all proportions and with dilute alcohol up to 55% by volume; immiscible with ether, chloroform, acetone, benzene, solvent hexane or turpentine oil.

Uses—To produce a brown color in elixirs, syrups and other preparations.

Flavoring Agents

Flavor

The word flavor refers to a mixed sensation of taste, touch, smell, sight and sound, all of which combine to produce an infinite number of gradations in the perception of a substance. The four primary tastes—*sweet*, *bitter*, *sour* and *saline*—appear to be the result partly of physicochemical and partly of psychological action. Taste buds (Fig 66-1), located mainly on the tongue, contain very sensitive nerve endings that react, in the presence of moisture, with the flavors in the mouth and as a result of physicochemical activity electrical impulses are produced and transmitted via the seventh, ninth and tenth cranial nerves to the areas of the brain which are devoted to the perception of taste. Some of the taste buds are specialized in their function, giving rise to areas on the tongue which are sensitive to only one type of taste. The brain, however, usually perceives taste as a composite sensation, and accordingly the components of any flavor are not readily discernible. Children have more taste buds than adults, hence are more sensitive to tastes.

Taste partly depends on the ions which are produced in the mouth, but psychologists have demonstrated that sight (color) and sound also play a definite role when certain reflexes become conditioned through custom and association of sense perceptions. Thus, in the classic experiments of Pavlov demonstrating "conditioned reflexes," the ringing of a bell or the showing of a circle of light caused the gastric juices of a dog to flow although no food was placed before it, and much of the enjoyment derived from eating celery is due to its crunchy crispness as the fibrovascular bundles are crushed. The effect of color is just as pronounced; oleomargarine is unpalatable to most people when it is uncolored, but once the dye has been incorporated gourmets frequently cannot distinguish it from butter. Color and taste must coincide, eg, cherry flavor is associated with a red color.

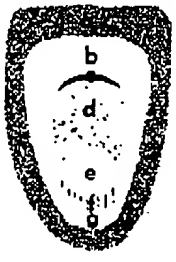


Fig 66-1. Upper Surface of the tongue. a: Taste receptors for all tastes; b: sweet, salty and sour; c: salty and sour; d: sour only; e: no taste sensation; f: sweet and sour and g: bitter, sweet and sour (adapted from Crocker EC: *Flavor*, McGraw-Hill, New York, 22, 1945).

A person suffering from a head cold finds his food much less palatable than usual because his sense of smell is impaired, and, if the nostrils are held closed, raw onions taste sweet and it is much easier to ingest castor oil and other nauseating medicines. The volatility of a substance is an important factor that is influenced by the warmth and moisture of the mouth since the more volatile a compound, the more pronounced its odor. The sense of smell detects very minute amounts of material and is usually much more sensitive in detecting the presence of volatile chemicals, but the tongue is able to detect infinitesimal amounts of some vapors if it is protruded from the mouth so that solution of the gases in the saliva may take place. In this manner traces of sulfur dioxide can be detected in the air since it dissolves in the saliva and creates a sour taste.

Flavors described as hot are those that exert a mild counterirritant effect on the mucosa of the mouth, those that are astringent and pucker the mouth contain tannins and acids that produce this effect by reacting with the lining of the mouth and wines possess a bouquet due to the odor of the volatile constituents. Indian turnip (Jack-in-the-pulpit) owes its flavor largely to the stinging sensation caused by the minute acicular crystals of calcium oxalate which penetrate the mucous membrane.

Other physiological and physical factors that also may affect taste are coarseness or grittiness due to small particles, eg, ion-exchange resins. Antidiarrheal preparations have a chalky taste. Menthol imparts a cool taste because it affects the coldness receptors. Mannitol gives a cool sensation when it dissolves because its negative of heat of solution will cause the temperature to drop. For this reason, mannitol often is used as the base for chewable tablets.

There is a definite threshold of taste for every substance, which varies somewhat with the individual and with the environment. The experienced chef tastes his delicacies at the temperature at which they will be served since heat and cold alter the flavor of many preparations. Thus, lemon

loses its sour taste entirely at an elevated temperature and other flavors become almost nonvolatile, tasteless and odorless when cooled sufficiently. In addition to the influence of temperature, the sensitivity of each individual must be considered. For example, it has been determined by experiment that the amount of sugar that can just be detected by the average individual is about 7 mg. However, this amount cannot be tasted by some and it is definitely sweet to others.

People are more sensitive to odor than to taste. There are about 10,000 to 30,000 identifiable scents, of which the average person can identify about 4000. Women are more sensitive to odors than men. Additional insights can be obtained by reading Cagan RH, Kare MR: *Biochemistry of Taste and Olfaction*, Academic, 1981, and Beidler LM (ed): *Handbook of Sensory Physiology*, vol IV, pts 1 and 2, Springer-Verlag, 1971.

Preservation of Flavors—Most monographs of official products contain specific directions for storage. Proper methods of storage are essential to prevent deterioration which in many instances results in destruction of odor and taste. Under adverse conditions undesirable changes occur due to one or a combination of the following: enzymatic activity, oxidation, change in moisture content, absorption of odors, activity of microorganisms and effects of heat and light. In certain products some of the changes wrought by these factors are desirable, as when esters are formed due to the activity of enzymes and when blending and mellowing results from the interchange of the radicals of esters (*transesterification*).

One method for protecting readily oxidizable substances, such as lemon oil, from deteriorating, and thus preserving their original delicate flavor, is to microencapsulate them by spray-drying. The capsules containing the flavors then are enclosed in various packaged products (eg, powdered gelatins) or tablets which are flavored deliciously when the capsule is disintegrated by mixing and warming with water or saliva.

Correlation of Chemical Structure with Flavor and Odor—The compounds employed as flavors in vehicles vary considerably in their chemical structure, ranging from simple esters (methyl salicylate), alcohols (glycerin) and aldehydes (vanillin) to carbohydrates (honey) and the complex volatile oils (anise oil). Synthetic flavors of almost any desired type are now available. These frequently possess the delicate flavor and aroma of the natural products and also the desirable characteristics of stability, reproducibility and comparatively low cost. Synthetic products such as cinnamaldehyde and benzaldehyde, first officially recognized when several of the essential oils became scarce during World War II, have been used widely.

There is a close relationship between chemical structure and taste. Solubility, the degree of ionization and the type of ions produced in the saliva definitely influence the sensation interpreted by the brain.

Sour taste is caused by hydrogen ions and it is proportional to the hydrogen-ion concentration and the lipid solubility of the compound. It is characteristic of acids, tannins, alum, phenols and lactones. Saltiness is due to simultaneous presence of anions and cations, eg, KBr, NH_4Cl and sodium salicylate. High-molecular-weight salts may have a bitter taste. Sweet taste is due to polyhydroxy compounds, polyhalogenated aliphatic compounds and α-amino acids. Amino and amide groups, especially if the positive effect is balanced by the proximity of a negative group, may produce a sweet taste. Sweetness increases with the number of hydroxy groups, possibly due to increase in solubility. Imides such as saccharin and sulfamates such as cyclamates are intensely sweet. Cyclamates have been removed from the market because they reportedly cause bladder tumors in rats. Free bases such as alkaloids and amides such as amphetamines give bitter tastes. Polyhydroxy compounds with a molecular weight greater than 300, halogenated substances and aliphatic thio compounds also may have bitter tastes. Unsaturation frequently bestows a sharp, biting odor and taste upon compounds.

No precise relationship between chemical structure and odor has been found. There are no primary odors, and odors blend into each other. Polymerization reduces or destroys odor; high valency gives odor and unsaturation enhances odor. A tertiary carbon atom often will give a camphoraceous odor, esters and lactones have a fruity odor and ketones have a pleasant odor. Strong odors often are accompanied by volatility and chemical reactivity.

Selection of Flavors

The proper selection of flavors for disguising nauseating medicines aids in their ingestion. Occasionally, sensitive patients have become nauseated sufficiently to vomit at the thought of having to take disagreeable medication, and it is particularly difficult to persuade children to continue to use and retain distasteful preparations. There is a need to know the allergies and idiosyncrasies of the patient; thus, it is foolish to use a chocolate-flavored vehicle for the patient who dislikes the flavor or who is allergic to it, notwithstanding the fact that this flavor is generally acceptable.

Flavoring Methodology

Each flavoring problem is unique and requires an individual solution. The problem of flavoring is further complicated because flavor and taste depend on individual preferences. In solving flavoring problems the following techniques have been used:

1. *Blending*—Fruit flavors blend with sour taste; bitter tastes can be blended with salty, sweet and sour tastes; salt reduces sourness and increases sweetness: chemicals such as vanillin, monosodium glutamate and benzaldehyde are used for blending.
2. *Overshadow*—Addition of a flavor whose intensity is longer and stronger than the obvious taste, eg, methyl salicylate, glycyrrhiza and oleoresins.
3. *Physical*—Formation of insoluble compounds of the offending drug, eg, sulfonamides; emulsification of oils; effervescence, eg, magnesium citrate solution; high viscosity of fluids to limit contact of drug with the tongue, and mechanical procedures such as coating tablets, are physical methods to reduce flavoring problems.
4. *Chemical*—Adsorption of the drug on a substrate, or formation of a complex of the drug with ion-exchange resins or complexing agents.
5. *Physiological*—The taste buds may be anesthetized by menthol or mint flavors.

Flavors, as used by the pharmacist in compounding prescriptions, may be divided into four main categories according to the type of taste which is to be masked, as follows:

1. *Salty Taste*—Cinnamon syrup has been found to be the best vehicle for ammonium chloride, and other salty drugs such as sodium salicylate and ferric ammonium citrate. In a study of the comparative efficiency of flavoring agents for disguising salty taste, the following additional vehicles were arranged in descending order of usefulness: orange syrup, citric acid syrup, cherry syrup, cocoa syrup, wild cherry syrup, raspberry syrup, glycyrrhiza elixir, aromatic elixir and glycyrrhiza syrup. The last-named is particularly useful as a vehicle for the salines by virtue of its colloidal properties and the sweetness of both glycyrrhizin and sucrose.
2. *Bitter Taste*—Cocoa syrup was found to be the best vehicle for disguising the bitter taste of quinine bisulfate, followed, in descending order of usefulness, by raspberry syrup, cocoa syrup, cherry syrup, cinnamon syrup, compound sarsaparilla syrup, citric acid syrup, licorice syrup, aromatic elixir, orange syrup and wild cherry syrup.
3. *Acrid or Sour Taste*—Raspberry syrup and other fruit syrups are especially efficient in masking the taste of sour substances such as hydrochloric acid. Acacia syrup and other mucilaginous vehicles are best for disguising the acrid taste of substances, such as capsicum, since they tend to form a colloidal protective coating over the taste buds of the tongue. Tragacanth, unlike acacia, may be used in an alcoholic vehicle.

4. *Oily Taste*—Castor oil may be made palatable by emulsifying with an equal volume of aromatic rhubarb syrup or with compound sarsaparilla syrup. Cod liver oil is disguised effectively by adding wintergreen oil or peppermint oil. Lemon, orange and anise or combinations of these are also useful. It is better to mix most of the flavor with the oil before emulsifying it, and then the small remaining quantity can be added after the primary emulsion is formed.

Those flavors that are most pleasing to the majority of people are associated with some stimulant of a physical or physiological nature. This may be a central nervous stimulant such as caffeine, which is the reason so many enjoy tea and coffee as a beverage, or it may be a counterirritant such as one of the spices that produce a "biting" sensation or an agent which "tickles" the throat such as soda water. Sherry owes its sharp flavor to its acetaldehyde content, and some of the volatile oils contain terpenes that are stimulating to the mucous surfaces.

Selection of Vehicles

Too few pharmacists realize the unique opportunity they have in acquainting physicians with a knowledge of how to increase both the palatability and efficacy of their prescribed medicines through the judicious selection of vehicles. Because of the training a pharmacist receives, his knowledge of the characteristics of various pharmaceuticals and therapeutic agents and his technique and skill in preparing elegant preparations are well-developed, so that he is qualified admirably to advise concerning the proper use of vehicles.

A large selection of flavors is available as well as a choice of colors, so that one may prescribe a basic drug for a prolonged period, but by changing the vehicle from time to time, the taste and appearance are so altered that the patient does not tire of the prescription or show other psychological reactions to it.

The statement of the late Dr Bernard Fantus that "the best solvent is the best vehicle" helps to explain the proper use of a flavoring vehicle. For example, a substance that is soluble in alcohol, eg, phenobarbital, will not leave an alcoholic vehicle readily to dissolve in the aqueous saliva.

Waters—These are the simplest of the vehicles and are available with several flavors. They contain no sucrose, a fact to be considered at times, since sucrose under certain circumstances may be undesirable. They are likewise nonalcoholic, another fact which frequently influences vehicle selection.

Elixirs—These have added sweetness that waters lack, and they usually contain alcohol, which imparts an added sharpness to the flavor of certain preparations, making the latter more pleasing to the taste. Elixirs are suitable for alcohol-soluble drugs.

Syrups—These vehicles, like elixirs, offer a wide selection of flavors and colors from which to choose. Their specific value, however, lies particularly in the fact that they are intensely sweet and contain little or no alcohol, a combination which makes them of singular value as masking agents for water-soluble drugs.

Vehicles consisting of a solution of pleasantly flavored volatile oils in syrup or glycerin (1:500) have been employed successfully in producing uniform and stable preparations. These vehicles are prepared by adding 2 mL of the volatile oil, diluted with 6 mL of alcohol, to 500 mL of glycerin or syrup, which has been warmed gently. The solution is added a little at a time with continuous shaking, and then sufficient glycerin or syrup is added to make 1000 mL, and mixed well.

Alcohol solutions of volatile oils are sometimes used as "stock solutions" for flavoring pharmaceuticals.

A listing of substances, most of them official, used as flavors, flavored vehicles or as sweeteners, is given in Table I. Additional information on flavoring ingredients may be obtained in Furia TE, Bellanca A: *Fenaroli's Handbook of Flavor Ingredients*, Chemical Rubber, Cleveland, 1971.

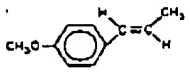
Table I—Flavoring Agents

Acacia syrup	Honey
Anethole	Iso-Alcoholic elixir
Anise oil	Lavender oil
Aromatic elixir	Lemon oil
Benzaldehyde	Lemon tincture
Benzaldehyde elixir, compound	Mannitol
Caraway	Methyl salicylate
Caraway oil	Nutmeg oil
Cardamom oil	Orange, bitter, elixir
Cardamom seed	Orange, bitter, oil
Cardamom spirit, compound	Orange flower oil
Cardamom tincture, compound	Orange flower water
Cherry juice	Orange oil
Cherry syrup	Orange peel, bitter
Cinnamon	Orange peel, sweet, tincture
Cinnamon oil	Orange spirit, compound
Cinnamon water	Orange syrup
Citric acid	Peppermint
Citric acid syrup	Peppermint oil
Clove oil	Peppermint spirit
Cocoa	Peppermint water
Cocoa syrup	Phenylethyl alcohol
Coriander oil	Raspberry juice
Dextrose	Raspberry syrup
Eriodictyon	Rosemary oil
Eriodictyon fluidextract	Rose oil
Eriodictyon syrup, aromatic	Rose water
Ethyl acetate	Rose water, stronger
Ethyl vanillin	Saccharin
Fennel oil	Saccharin calcium
Ginger	Saccharin sodium
Ginger fluidextract	Sarsaparilla syrup, compound
Ginger oleoresin	Sorbitol solution
Glucose	Spearmint
Glycerin	Spearmint oil
Glycyrrhiza	Sucrose
Glycyrrhiza elixir	Syrup
Glycyrrhiza extract	Thyme oil
Glycyrrhiza extract, pure	Tolu balsam
Glycyrrhiza fluidextract	Tolu balsam syrup
Glycyrrhiza syrup	Vanilla
	Vanilla tincture
	Vanillin
	Wild cherry syrup

Acacia Syrup—see page 1301.

Anethole

Benzene, 1-methoxy-4-(1-propenyl)-, (*E*)-, Anethol; Anise Camphor



(*E*)-*p*-Propenylanisole [4180-23-8] $C_{10}H_{12}O$ (148.20); obtained from anise oil and other sources, or prepared synthetically.

Preparation—It is the principal constituent of anise and fennel oil and usually is obtained from these sources by fractionating and chilling the proper fraction whereby it crystallizes out.

Description—Colorless or faintly yellow liquid at or above 23°; aromatic odor of anise and a sweet taste; affected by light; specific gravity 0.982 to 0.988; distils completely 231 to 237° and congeals at not less than 20°; its alcohol solution is neutral to litmus.

Solubility—Very slightly soluble in water; freely soluble in alcohol; miscible with chloroform or ether; yields a clear solution with 2 volumes of alcohol.

Uses—A *flavoring agent*. Its uses are similar to those of anise oil. It sometimes is sold as *Synthetic* or *Artificial Anise Oil* for flavoring and is a licorice-like flavor used in *Diphenhydramine Hydrochloride Elixir*.

Anise Oil

Anised Oil; Star Anise Oil

The volatile oil distilled with steam from the dried, ripe fruit of *Pimpinella anisum* Linné (Fam *Umbelliferae*) or from the dried, ripe fruit of *Illicium verum* Hooker filius (Fam *Magnoliaceae*).

Note—If solid material has separated, carefully warm the oil until it is completely liquefied, and mix it before using.

Constituents—The official oil varies somewhat in composition, depending upon whether it was obtained from *Pimpinella anisum* or the star anise, *Illicium verum*. *Anethole* is the chief constituent of both oils, occurring to the extent of 80 to 90%. *Methyl chavicol*, an isomer of anethole, and *anisic ketone* [$C_{10}H_{12}O_2$] are also found in both oils, as are small amounts of many other constituents.

Description—Colorless or pale yellow, strongly refractive liquid, having the characteristic odor and taste of anise; specific gravity 0.978 to 0.988; congeals not below 15°.

Solubility—Soluble in 3 volumes of 90% alcohol.

Uses—Extensively as a *flavoring agent*, particularly for licorice candies. It has been given as a *carminative* in a dose of about 0.1 mL.

Aromatic Elixir—page 1302.

Aromatic Elixir, Red—RPS-15, page 1240.

Benzaldehyde

Artificial Essential Almond Oil

Benzaldehyde [100-52-7] C_7H_6O (106.12).

Preparation—By the interaction of benzal chloride with lime in the presence of water. Benzal chloride is obtained by treating boiling toluene with chlorine.

Description—Colorless, strongly refractive liquid, having an odor resembling that of bitter almond oil, and a burning aromatic taste; affected by light; specific gravity 1.041 to 1.046; boils about 180°, solidifies about −56.5° and on exposure to air it gradually oxidizes to benzoic acid.

Solubility—Dissolves in about 350 volumes of water; miscible with alcohol, ether, chloroform or fixed and volatile oils.

Uses—In place of bitter almond oil for *flavoring* purposes; it is much safer than the latter because it contains no hydrocyanic acid. It also is used extensively in *perfumery* and in the manufacture of dyestuffs and many other organic compounds, such as aniline, acetanilid or mandelic acid.

Compound Benzaldehyde Elixir—*Preparation:* Dissolve benzaldehyde (0.5 mL) and vanillin (1 g) in alcohol (50 mL); add syrup (400 mL), orange flower water (150 mL) and sufficient purified water, in several portions, shaking the mixture thoroughly after each addition, to make the product measure 1000 mL; then filter, if necessary, until the product is clear. *Alcohol Content:* 3 to 5%. *Uses:* A useful vehicle for administering bromides and other salts, especially when a low alcoholic content is desired.

Camphor Water—RPS-13, page 436.

Caraway

Carum; Caraway Seed; Caraway Fruit; Kümmel

The dried ripe fruit of *Carum carvi* Linné (Fam *Umbelliferae*).

Constituents—About 5% of *volatile oil*, with a little *fixed oil* and other constituents.

Uses—A *flavor*. It also has been used empirically as a *carminative* and *stimulant*.

Caraway Oil [Oleum Cari]—A volatile oil distilled from the dried, ripe fruit of *Carum carvi* Linné (Fam *Umbelliferae*); yields not less than 50% (*v/v*) of $C_{10}H_{14}O$ (carvone). The chief odoriferous component of the oil is the ketone *d-carvone* [$C_{10}H_{14}O$], which is the optical isomer of the levorotatory variety occurring in spearmint oil. The remainder of the oil consists mainly of the terpene *d-limonene* [$C_{10}H_{16}$]. Colorless or pale yellow liquid, with the characteristic odor and taste of caraway; specific gravity 0.900 to 0.910. *Uses:* In making caraway water and as a flavor and *carminative* in other pharmaceutical preparations.

Cardamom Seed

Cardamom Fruit; Cardamom; Ceylon or Malabar Cardamom

The dried ripe seed of *Elettaria cardamomum* (Linné) Maton (Fam. *Zingiberaceae*).

It should be removed recently from the capsule.

Constituents—A *volatile oil*, the yield of which is 1.3% from Malabar Ceylon Seeds and 2.6% from Mysore Ceylon Seeds. *Fixed oil* is present to the extent of 10%, also starch, mucilage, etc.

Uses—A *flavor*. For many years it was employed empirically as a *carminative*.

Cardamom Oil—The volatile oil distilled from the seed of *Elettaria cardamomum* (Linné) Maton (Fam *Zingiberaceae*). Varieties of the oil contain *d-α-terpineol* [$C_{10}H_{17}OH$] both free and as the acetate, 5 to 10% *cineol* [$C_{10}H_{18}O$] and *limonene* [$C_{10}H_{16}$]. The Ceylon Oil, however, contains the alcohol *4-terpineol* (*4-carbomenthenol*) [$C_{10}H_{17}OH$], the terpenes *terpinene* and *sabinene*, and *acetic* and *formic acids*, probably combined as esters. Colorless or very pale yellow liquid possessing the aromatic, penetrating and somewhat camphoraceous odor of cardamom, and a persistently pungent, strongly aromatic taste; affected by light. Specific gravity 0.917 to 0.947; miscible with alcohol; dissolves in 5 volumes of 70% alcohol. *Uses:* A *flavor*.

Cardamom Tincture, Compound—page 1302.

Cherry Juice—page 1320.

Cherry Syrup—page 1301.

Cinnamon

Saigon Cinnamon; True Cinnamon; Saigon Cassia

The dried bark of *Cinnamomum loureirii* Nees (Fam. *Lauraceae*).

It contains, in each 100 g, not less than 2.5 mL of volatile oil.

Uses—A *flavoring agent*. Formerly, it was used as a carminative.

Cinnamon Oil [Cassia Oil; Oil of Chinese Cinnamon]—The volatile oil distilled with steam from the leaves and twigs of *Cinnamomum cassia* (Nees) Nees ex Blume (Fam *Lauraceae*), rectified by distillation; contains not less than 80%, by volume, of the total aldehydes of cinnamon oil. Cinnamaldehyde is the chief constituent. Yellowish or brownish liquid, becoming darker and thicker on aging or exposure to the air, and having the characteristic odor and taste of cassia cinnamon; specific gravity 1.045 to 1.063. Soluble in an equal volume of alcohol, 2 volumes of 70% alcohol or an equal volume of glacial acetic acid. *Uses:* A *flavor*. It formerly was used in a dose of 0.1 mL for flatulent colic.

Cocoa

Cacao USP XVI; Prepared Cocoa; Powdered Cocoa; Cocoa Powder; Medium-Fat Cocoa

A powder prepared from the roasted, cured kernels of the ripe seed of *Theobroma cacao* Linné (Fam *Sterculiaceae*).

It yields 10 to 22% of nonvolatile, ether-soluble extractive.

Preparation—The cocoa bean is dark as the result of a fermentation and roasting process which it undergoes. *Plain chocolate* consists of shelled cocoa beans (*cocoa nibs*) ground to a smooth paste which forms a hard cake when it cools because of the high fat content (50 to 58%).

It is the food prepared by pulverizing the residue remaining after part of the fat has been removed by expression from plain chocolate. It may be flavored by the addition of ground spice, ground vanilla bean, vanillin, ethylvanillin, coumarin, salt and other flavors as long as they do not imitate the flavor of chocolate, milk or butter. Three types are recognized depending on fat content: *breakfast cocoa* or *high fat cocoa* (22% minimum), *cocoa* or *medium-fat cocoa* (10 to 22%) and *low-fat cocoa* (less than 10%).

Sweet chocolate is plain chocolate plus added sugar and flavor (usually vanilla).

Milk chocolate is a mixture of sweet chocolate and milk powder or other dairy product. Chocolate and the products described above contain the purines theobromine and caffeine, and considerable quantities of fat (cocoa butter or theobroma oil), as well as protein and starch. These factors are lowered in sweet chocolate because of the large amount of added sugar (more than 50% of the final product).

Description—Weak reddish to purplish brown to moderate brown powder having a chocolate-like odor and taste, free from sweetness.

Uses—A food and pharmaceutically as a flavor in tablets, syrups, pill and tablet coatings, troches, etc.

Cocoa Syrup—page 1301.

Coriander—page 1299.

Coriander Oil

The volatile oil distilled with steam from the dried ripe fruit of *Coriandrum sativum* Linné (Fam *Umbelliferae*).

Constituents—The alcohol *d-linalool* (formerly termed "*coriandrol*") is the chief constituent of this oil, occurring in amounts varying from 60 to 80%. Other constituents include *l-borneol, geraniol, pinenes, terpinenes* and *p-cymene*.

Description—Colorless or pale yellow liquid, having the characteristic odor and taste of coriander; specific gravity 0.863 to 0.875.
Solubility—Soluble in 3 volumes of 70% alcohol.

Uses—A flavoring agent. It formerly was employed in a dose of 0.1 mL as a *carminative*.

Denatonium Benzoate—page 1321.

Eriodictyon

Consumptives' Weed; Mountain Balm; Yerba Santa

The dried leaf of *Eriodictyon californicum* (Hooker et Arnott) Torrey (Fam *Hydrophyllaceae*).

Constituents—A bitter *resin, volatile oil, eriodictyonone* [$C_{16}H_{14}O_6$, also called *homoeriodictyol*], *fixed oil, tannin, gum*, etc.

Uses—A pharmaceutical necessity. It is used in the preparation of *Eriodictyon Fluidextract*.

Eriodictyon Fluidextract [Yerba Santa Fluidextract]—*Preparation:* Using Eriodictyon (in moderately coarse powder, 1000 g), prepare the fluidextract by Process A (page 1543), using a mixture of 4 volumes of alcohol and 1 volume of water as the menstruum. Macerate the drug during 48 hr, then percolate at a moderate rate and reserve the first 800 mL of percolate. *Alcohol Content:* 57 to 62%. *Uses:* A peculiar, aromatic *flavor* used in syrups and elixirs, especially for masking the taste of bitter drugs like quinine. Because of its resinous character it requires an alkali to render it soluble in aqueous mixtures.

Eriodictyon Syrup, Aromatic—page 1301.

Ethyl Acetate

Acetic acid, ethyl ester; Acetic Ether

$CH_3COOC_2H_5$

Ethyl acetate [141-78-6] $C_4H_8O_2$ (88.11).

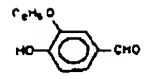
Preparation—By slow distillation of a mixture of alcohol and acetic acid in the presence of sulfuric acid.

Description—Transparent, colorless liquid with a fragrant and refreshing, slightly acetous odor, and a peculiar acetous, burning taste; specific gravity 0.894 to 0.898; distills 76 to 77.5°.
Solubility—1 mL in about 10 mL of water; miscible with alcohol, acetone, ether, chloroform or fixed and volatile oils.

Uses—Chiefly as a *flavoring agent*. It is used industrially in artificial fruit essence, as a *solvent* for nitrocellulose varnishes and lacquers and as a solvent in organic chemistry.

Ethyl Vanillin

Benzaldehyde, 3-ethoxy-4-hydroxy-, Bourbanal; Ethovan; Vanillal; Vanirome



3-Ethoxy-4-hydroxybenzaldehyde [121-32-4] $C_9H_{10}O_3$ (166.18).

Preparation—By reacting *o*-ethoxyphenol with formaldehyde and *p*-nitrosodimethylaniline in the presence of aluminum and water.

Description—Fine, white or slightly yellowish crystals; odor and taste similar to vanillin; affected by light; solutions are acid to litmus; melts about 77°.
Solubility—1 g in about 100 mL of water at 50°; freely soluble in alcohol, chloroform, ether or solutions of fixed alkali hydroxides.

Uses—A *flavor*, like vanillin, but stronger.

Eucalyptus Oil

The volatile oil distilled with steam from the fresh leaf of *Eucalyptus globulus* Labillardière or of some other species of *Eucalyptus* L'Heritier (Fam *Myrtaceae*). It contains not less than 70% of $C_{10}H_{18}O$ (eucalyptol).

Constituents—The most important constituent is *eucalyptol (cineol)*. Other compounds include *d-a-pinene, globulol, pinocarveol, pinocarvone* and several aldehydes.

Description—Colorless or pale yellow liquid, having a characteristic, aromatic, somewhat camphoraceous odor, and a pungent, spicy, cooling taste; specific gravity 0.905 to 0.925 at 25°.
Solubility—Soluble in 5 volumes of 70% alcohol.

Uses—A *flavoring agent* and an *expectorant* in chronic bronchitis. It also has *bacteriostatic* properties. This oil may be toxic.

Fennel Oil

The volatile oil distilled with steam from the dried ripe fruit of *Foeniculum vulgare* Miller (Fam *Umbelliferae*).

Note—If solid material has separated, carefully warm the oil until it is completely liquefied, and mix it before using.

Constituents—*Anethole* [$C_{10}H_{12}O$] is the chief constituent, occurring to the extent of 50 to 60%. Some of the other constituents are *d*-pinene, phellandrene, dipentene, fenchone, methylchavicol, anisaldehyde and anisic acid.

Description—Colorless or pale yellow liquid, having the characteristic odor and taste of fennel; specific gravity 0.953 to 0.973; congealing temperature is not below 3°.
Solubility—Soluble in 8 volumes of 80% alcohol or in 1 volume of 90% alcohol.

Uses—A flavoring agent. It formerly was employed in a dose of 0.1 mL as a *carminative*.

Glycyrrhiza

Licorice Root; Liquorice Root; Sweetwood; Italian Juice Root; Spanish Juice Root

The dried rhizome and roots of *Glycyrrhiza glabra* Linné, known in commerce as Spanish Licorice, or of *Glycyrrhiza glabra* Linné var *glandulifera* Waldstein et Kitaibel, known in commerce as Russian Licorice, or of other varieties of *Glycyrrhiza glabra* Linné, yielding a yellow and sweet wood (Fam. *Leguminosae*).

Constituents—This well-known root contains 5 to 7% of the sweet principle *glycyrrhizin*, or *glycyrrhizic acid* which is 50 times as sweet as cane sugar. There also is present an oleoresinous substance to which its slight acridity is due. If alcohol or an alkali is used as a menstruum for the root and the preparation not treated to deprive it of acridity, it will have a disagreeable aftertaste. For this reason boiling water is used for its extraction in both the extract and the fluidextract.

Description—The USP/NF provides descriptions of *Unground Spanish and Russian Glycyrrhizas, Histology* and *Powdered Glycyrrhiza*.

Uses—Valuable in pharmacy chiefly for its *sweet flavor*. It is one of the most efficient substances known for masking the taste of bitter substances, like quinine. Acids precipitate the glycyrrhizin and should not be added to mixtures in which glycyrrhiza is intended to mask disagreeable taste. Most of the imported licorice is used

by tobacco manufacturers to flavor tobacco. It also is used in making candy.

Pure Glycyrrhiza Extract [Pure Licorice Root Extract]—*Preparation:* Moisten 1000 g of glycyrrhiza, in granular powder, with boiling water, transfer it to a percolator, and percolate with boiling water until the glycyrrhiza is exhausted. Add enough diluted ammonia solution to the percolate to impart a distinctly ammoniacal odor, then boil the liquid under normal atmospheric pressure until it is reduced to a volume of about 1500 mL. Filter the liquid, and immediately evaporate the filtrate until the residue has a pilular consistency. Pure extract of glycyrrhiza differs from the commercial extract in that it is almost completely soluble in aqueous mixtures. The large amount of filler used in the commercial extract to give it firmness renders it unfit to use as a substitute for the pure extract. *Description:* Black, pilular mass having a characteristic, sweet taste. *Uses:* A *flavoring agent.* One of the ingredients in *Aromatic Cascara Sagrada Fluidextract.*

Glycyrrhiza Fluidextract [Licorice Root Fluidextract; Liquid Extract of Liquorice]—*Preparation:* To 1000 g of coarsely ground glycyrrhiza add about 3000 mL of boiling water, mix, and allow to macerate in a suitable, covered percolator for 2 hr. Then allow the percolation to proceed at a rate of 1 to 3 mL/min, gradually adding boiling water until the glycyrrhiza is exhausted. Add enough diluted ammonia solution to the percolate to impart a distinctly ammoniacal odor, then boil the liquid actively under normal atmospheric pressure until it is reduced to a volume of about 1500 mL. Filter the liquid, evaporate the filtrate on a steam bath until the residue measures 750 mL, cool, gradually add 250 mL of alcohol and enough water to make the product measure 1000 mL and mix. *Alcohol Content:* 20 to 24%, by volume. *Uses:* A pleasant *flavor* for use in syrups and elixirs to be employed as vehicles and correctives.

Glycyrrhiza Elixir—page 1302.
Glycyrrhiza Syrup—page 1302.
Honey—page 1302.
Hydriodic Acid Syrup—page 1302.
Iso-Alcoholic Elixir—page 1328.

Lavender Oil

Lavender Flowers Oil

The volatile oil distilled with steam from the fresh flowering tops of *Lavandula officinalis* Chaix ex Villars (*Lavandula vera* DeCandolle) (Fam *Labiatae*) or produced synthetically. It contains not less than 35% of esters calculated as $C_{12}H_{20}O_2$ (linalyl acetate).

Constituents—It is a product of considerable importance in perfumery. *Linalyl acetate* is the chief constituent. *Cineol* appears to be a normal constituent of English oils. Other constituents include *amyl alcohol, d-borneol* (small amount); *geraniol, lavandulol* ($C_{10}H_{18}O$); *linaloöl; neral; acetic, butyric, valeric,* and *caproic acids* (as esters); traces of *d-pinene, limonene* (in English oils only) and the sesquiterpene *caryophyllene; ethyl n-amyl ketone;* an aldehyde (probably *valeric aldehyde*) and *coumarin.*

Description—Colorless or yellow liquid, having the characteristic odor and taste of lavender flowers; specific gravity 0.875 to 0.888.
Solubility—1 volume dissolves in 4 volumes of 70% alcohol.

Uses—Primarily as a *perfume.* It formerly was used in doses of 0.1 mL as a *carminative.*

Lemon Oil

The volatile oil obtained by expression, without the aid of heat, from the fresh peel of the fruit of *Citrus limon* (Linné) Burmann filius (Fam *Rutaceae*), with or without the previous separation of the pulp and the peel. The total aldehyde content, calculated as citral ($C_{10}H_{16}O$), is 2.2–3.8% for California-type oil, and 3.0–5.5% for Italian-type oil.

Note—Do not use oil that has a terebinthine odor.

Constituents—From the standpoint of odor and flavor, the most noteworthy constituent is the aldehyde *citral,* which is present to the extent of about 4%. About 90% of *d-limonene* is present; small amounts of *l-α-pinene, β-pinene, camphene, β-phellandrene* and γ-terpinene also occur. About 2% of a solid, nonvolatile substance called *citroptene, limettin* or *lemon-camphor,* which is dissolved out of the peel, also is present. In addition, there are traces of several other compounds: *α-terpineol;* the *acetates of linaloöl* and *geraniol; citronellal, octyl* and *nonyl aldehydes;* the sesquiterpenes *bisabolene* and *cadinene* and the ketone *methylheptenone.*

When fresh, the oil has the fragrant odor of lemons. Because of the instability of the terpenes present, the oil readily undergoes deterioration by oxidation, acquiring a terebinthinate odor.

Description—Pale yellow to deep yellow or greenish yellow liquid, with the characteristic odor and taste of the outer part of fresh lemon peel; specific gravity 0.849 to 0.855.
Solubility—Soluble in 3 volumes of alcohol; miscible in all proportions with dehydrated alcohol, carbon disulfide or glacial acetic acid.

Uses—A *flavor* in pharmaceutical preparations and in certain candies and foods.

Methyl Salicylate

Benzoic acid, 2-hydroxy-, methyl ester; Gaultheria Oil; Wintergreen Oil; Betula Oil; Sweet Birch Oil; Teaberry Oil; Artificial Wintergreen Oil; Synthetic Wintergreen Oil

Methyl salicylate [119-36-8] $C_6H_4(OH)COOCH_3$ (152.15); produced synthetically or obtained by maceration and subsequent distillation with steam from the leaves of *Gaultheria procumbens* Linné (Fam *Ericaceae*) or from the bark of *Betula lenta* Linné (Fam *Betulaceae*).

Note—It must be labeled to indicate whether it was made synthetically or distilled from either of the plants mentioned above.

Preparation—Found naturally in gaultheria and betula oils and in many other plants but the commercial product is usually synthetic, made by esterifying salicylic acid with methyl alcohol in the presence of sulfuric acid and distilling.

Description—Colorless, yellowish or reddish liquid, having the characteristic odor and taste of wintergreen; specific gravity (synthetic) 1.180 to 1.185, (from gaultheria or betula), 1.176 to 1.182; boils between 219 to 224° with some decomposition.
Solubility—Slightly soluble in water; soluble in alcohol or glacial acetic acid.

Uses—A pharmaceutical necessity and *counterirritant* (local analgesic). As a pharmaceutical necessity, it is used to flavor the official *Aromatic Cascara Sagrada Fluidextract,* and it is equal in every respect to wintergreen oil or sweet birch oil. As a counterirritant, it is applied to the skin in the form of a liniment, ointment or cream; care should be exercised since salicylate is absorbed through the skin.

Caution—Because it smells like wintergreen candy, it is ingested frequently by children and has caused many fatalities. *Keep out of the reach of children.*

Dose—*Topical,* in lotions and solutions in 10 to 25% concentration.

Monosodium Glutamate

Glutamic acid, monosodium salt, monohydrate

[142-47-2] $C_5H_8NNaO_4 \cdot H_2O$ (187.13)

Preparation—From the fermentation of beet sugar or molasses or by hydrolysis of vegetable proteins.

Description—White, crystalline powder. The pentahydrate effloresces in air to form the monohydrate.
Solubility—Very soluble in water; sparingly soluble in alcohol.

Uses—Flavoring agent and perfume.

Nutmeg Oil

Myristica Oil NF XIII; East Indian Nutmeg Oil; West Indian Nutmeg Oil

The volatile oil distilled with steam from the dried kernels of the ripe seeds of *Myristica fragrans* Houttuyn (Fam *Myristicaceae*).

Constituents—It contains about 80% of *d-pinene* and *d-camphene,* 8% of *dipentene,* about 6% of the alcohols *d-borneol, geraniol, d-linaloöl* and *terpineol,* 4% of *myristicin,* 0.6% of *safrol,* 0.3% of *myristic acid* free and as esters. 0.2% of *eugenol* and *isoeugenol* and traces of the alcohol *terpineol-4,* a citral-like aldehyde and several acids, all present as esters.

Description—Colorless or pale yellow liquid having the characteristic odor and taste of nutmeg; specific gravity (East Indian Oil) 0.880 to 0.910. (West Indian Oil) 0.854 to 0.880.

Solubility—Soluble in an equal amount of alcohol; 1 volume of East Indian Oil in 3 volumes of 90% alcohol; 1 volume of West Indian Oil in 4 volumes of 90% alcohol.

Uses—Primarily as a *flavoring agent*. It is used for this purpose in *Aromatic Ammonia Spirit* (page 1539). The oil also is employed as a *flavor* in foods, certain alcoholic beverages, dentifrices and tobacco; to some extent, it also is used in perfumery. It *formerly* was used as a *carminative* and *local stimulant* to the gastrointestinal tract in a dose of 0.03 mL. In overdoses, it acts as a narcotic poison. *This oil is very difficult to keep and even if slightly terebinthinate is unfit for flavoring purposes.*

Orange Oil

Sweet Orange Oil

The volatile oil obtained by expression from the fresh peel of the ripe fruit of *Citrus sinensis* (Linné) Osbeck (Fam *Rutaceae*). The total aldehyde content, calculated as decanal ($C_{10}H_{20}O$), is 1.2 to 2.5%.

Note—Do not use oil that has a terebinthine odor.

Constituents—Consists of *d-limonene* to the extent of at least 90%; in the remaining 5 to 10% are the odorous constituents, among which, in samples of American origin, are *n-decylic aldehyde, citral, d-linalool, n-nonyl alcohol* and traces of *esters of formic, acetic, caprylic* and *capric* acids.

In addition to most of these compounds, Italian-produced oil contains *d-terpineol, terpinolene, α-terpinene* and *methyl anthranilate.*

Kept under the usual conditions it is very prone to decompose, and rapidly acquires a terebinthine odor.

Description—Intensely yellow orange or deep orange liquid, which possesses the characteristic odor and taste of the outer part of fresh sweet orange peel; specific gravity 0.842 to 0.846.

Solubility—Miscible with dehydrated alcohol and with carbon disulfide; dissolves in an equal volume of glacial acetic acid.

Uses—A *flavoring agent* in elixirs and other preparations.

Orange Flower Oil

Neroli Oil

The volatile oil distilled from the fresh flowers of *Citrus aurantium* Linné (Fam *Rutaceae*).

Constituents—*β-Ocimene, l-α-pinene, l-camphene, dipentene, l-linalool, geraniol, farnesol, d-terpineol, phenylethyl alcohol, neral, nerolidol, decylic aldehyde, jasmone, methyl anthranilate, indole, acetic esters of the alcohols* present and traces of *esters of benzoic, phenylacetic* and *palmitic acids.*

Description—Pale yellow, slightly fluorescent liquid, which becomes reddish brown on exposure to light and air; distinctive, fragrant odor, similar to that of orange blossoms, and an aromatic, at first sweet, then somewhat bitter, taste; may become turbid or solid at low temperatures; specific gravity 0.863 to 0.880; neutral to litmus paper; an alcoholic solution has a *violet fluorescence.*

Uses—A *flavor* and *perfume.* Several less valuable varieties of the oil are known commercially. These are designated as *Bigarade* (from the fresh flowers of bitter orange, the ordinary neroli oil), *Portugal* (from the fresh flowers of sweet orange) and *Petit-grain* (from the leaves and young shoots of the bitter orange). The finest variety is known as *Petale.*

Orange Flower Water—page 1300.

Sweet Orange Peel Tincture

Preparation—From sweet orange peel, which is the outer rind of the nonartificially colored, fresh, ripe fruit of *Citrus sinensis* (Linné) Osbeck (Fam *Rutaceae*), by Process M (page 1543). Macerate 500 g of the sweet orange peel (*Note—Exclude the inner, white portion of the rind*) in 900 mL of alcohol, and complete the preparation with alcohol to make the product measure 1000 mL. Use talc as the filtering medium.

The white portion of the rind must not be used, as the proportion of oil, which is only in the yellow rind, is reduced, and the bitter principle *hesperidin* is introduced.

Alcohol Content—62 to 72%.

Uses—A *flavor*, used in syrups, elixirs and emulsions. This tincture was introduced to provide a delicate orange flavor direct from the fruit instead of depending upon orange oil which so frequently is terebinthinate and unfit for use. The tincture keeps well.

Compound Orange Spirit

Contains, in each 100 mL, 25 to 30 mL of the mixed oils.

Orange Oil	200 mL
Lemon Oil	50 mL
Coriander Oil	20 mL
Anise Oil	5 mL
Alcohol, a sufficient quantity,	
To make	1000 mL

Mix the oils with sufficient alcohol to make the product measure 1000 mL.

Alcohol Content—65 to 75%.

Uses—A *flavor* for elixirs. An alcoholic solution of this kind permits the uniform introduction of small proportions of oils and also preserves orange and lemon oils from rapid oxidation. These two oils should be bought in small quantities by the pharmacist, since the spirit is made most satisfactorily from oils taken from bottles not previously opened. This will insure that delicacy of flavor which should always be characteristic of elixirs.

Orange Syrup

Syrup of Orange Peel

Contains, in each 100 mL, 450 to 550 mg of citric acid ($C_6H_8O_7$).

Sweet Orange Peel Tincture	50 mL
Citric Acid (anhydrous)	5 g
Talc	15 g
Sucrose	820 g
Purified Water, a sufficient quantity,	
To make	1000 mL

Triturate the talc with the tincture and citric acid, and gradually add 400 mL of purified water. Then filter, returning the first portions of the filtrate until it becomes clear, and wash the mortar and filter with enough purified water to make the filtrate measure 450 mL. Dissolve the sucrose in this filtrate by agitation, without heating, and add enough purified water to make the product measure 1000 mL. Mix and strain.

Note—Do not use syrup that has a terebinthine odor or taste or shows other indications of deterioration.

Alcohol Content—2 to 5%.

Uses—A pleasant, acidic vehicle.

Peppermint

American Mint; Lamb Mint; Brandy Mint

Consists of the dried leaf and flowering top of *Mentha piperita* Linné (Fam *Labiatae*).

Uses—The source of green color for *Peppermint Spirit* (page 798). The odor of fresh peppermint is due to the presence of about 2% of a volatile oil, much of which is lost on drying the leaves in air. It is cultivated widely both in the US and France. It formerly was used as a carminative.

Peppermint Oil—The volatile oil distilled with steam from the fresh overground parts of the flowering plant of *Mentha piperita* Linné (Fam *Labiatae*), rectified by distillation and neither partially nor wholly dementhotholized. It yields not less than 5% of esters, calculated as menthyl acetate [$C_{12}H_{22}O_2$], and not less than 50% of total menthol [$C_{10}H_{20}O$], free and as esters. *Constituents:* This is one of the most important of the group of volatile oils. The chief constituent is *Menthol* (page 765) which occurs in the levorotatory form; its ester, *menthyl acetate*, is present in a much smaller amount. Other compounds which are present include the ketone *menthone, piperitone, α-pinene, l-limonene, phellandrene, cadinene, menthyl isovalerate, isovaleric aldehyde, acetaldehyde, menthofuran, cineol,* an unidentified *lactone* [$C_{10}H_{16}O_2$] and probably *amyl acetate.* Colorless or pale yellow liquid, having a strong,

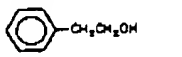
penetrating odor of peppermint and a pungent taste, followed by a sensation of cold when air is drawn into the mouth; specific gravity 0.896 to 0.908; 1 volume dissolves in 3 volumes of 70% alcohol. *Uses:* A *flavoring agent, carminative, antiseptic* and *local anesthetic.* It also is used extensively as a *flavor* in candy, chewing gum, etc.

Peppermint Spirit—page 798.

Peppermint Water—page 1300.

Phenylethyl Alcohol

Benzeneethanol; 2-Phenylethanol



Phenethyl alcohol [60 12 8] $C_8H_{10}O$ (122.17); occurs in a number of essential oils such as those of rose, neroli, hyacinth, carnation and others.

Description—Colorless liquid with a rose-like odor and a sharp, burning taste; solidifies at −27°; specific gravity 1.017 to 1.020.

Solubility—1 g in 60 mL of water; <1 mL of alcohol, chloroform or ether; very soluble in fixed oils, glycerin or propylene glycol; slightly soluble in mineral oil.

Uses—Introduced for use as an antibacterial agent in ophthalmic solutions, but it is of limited effectiveness.

It is used in *flavors*, as a *soap perfume* and in the preparation of synthetic oils of rose and similar flower oils. It is also a valuable perfume fixative.

Pine Needle Oil

Dwarf Pine Oil

The volatile oil distilled with steam from the fresh leaf of *Pinus mugo* Turra and its variety *pumilio* (Haenke) Zenari (Fam *Pinaceae*); contains 3 to 10%, by weight, of esters calculated as $C_{12}H_{20}O_2$ (bornyl acetate).

Constituents—It contains the terpenes *l-α-pinene, β-pinene, l-phellandrene, l-limonene, dipentene*, and possibly *sylvestrene*, the ester *bornyl acetate* and several unidentified terpene and sesquiterpene alcohols.

Description—Colorless to yellowish liquid, having a pleasant, aromatic odor and a bitter, pungent taste; specific gravity 0.853 to 0.871 at 25°.

Solubility—Dissolves in 4.5 to 10 volumes of 90% alcohol, often with turbidity.

Uses—Chiefly as a *perfume* and *flavoring agent.* It also is employed as an inhalant in bronchitis.

Raspberry Syrup—page 1302.

Rose Oil

Otto of Rose; Attar of Rose

The volatile oil distilled with steam from the fresh flowers of *Rosa gallica* Linné, *Rosa damascena* Miller, *Rosa alba* Linné, *Rosa centifolia* Linné and varieties of these species (Fam *Rosaceae*).

Constituents—From the quantitative standpoint the chief components are the alcohols *geraniol* [$C_{10}H_{18}O$] and *l-citronellol* [$C_{10}H_{20}O$]. The sesquiterpene alcohols *farnesol* and *nerol* occur to the extent of 1% and 5 to 10%, respectively. Together, the four alcohols constitute 70 to 75% of the oil. *Phenylethyl alcohol*, which comprises 1% of the oil, is an important odoriferous constituent. Other compounds present are *linalool, eugenol, nonyl aldehyde*, traces of *citral* and two solid hydrocarbons of the paraffin series.

Description—A colorless or yellow liquid, which has the characteristic odor and taste of rose; at 25° a viscous liquid; on gradual cooling it changes to a translucent, crystalline mass, which may be liquefied easily by warming; specific gravity 0.848 to 0.863 at 30° compared with water at 15°; 1 mL mixes with 1 mL of chloroform without turbidity; on the addition of 20 mL of 90% alcohol to this solution, the resulting liquid is neutral or acid to moistened litmus paper and deposits a crystalline residue within 5 min on standing at 20°.

Uses—Principally as a *perfume.* It is recognized officially for its use as an ingredient in *Rose Water Ointment* and cosmetics.

Stronger Rose Water

Triple Rose Water

A saturated solution of the odoriferous principles of the flowers of *Rosa centifolia* Linné (Fam *Rosaceae*), prepared by distilling the fresh flowers with water and separating the excess volatile oil from the clear, water portion of the distillate.

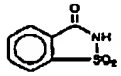
Note—When diluted with an equal volume of purified water, it may be supplied when *Rose Water* is required.

Description—Nearly colorless and clear liquid which possesses the pleasant odor and taste of fresh rose blossoms; must be free from empyreuma, mustiness and fungal growths.

Uses—An ingredient in *Rose Water Ointment.* It sometimes is prepared extemporaneously from concentrates or from rose oil, but such water is not official and rarely compares favorably with the fresh distillate from rose petals.

Saccharin

1,2-Benzisothiazol-3(2*H*)-one, 1,1-dioxide; Gluside; o-Benzosulfimide
Saxin (*Burroughs Wellcome*); Sweets (*Squibb*)



1,2-Benzisothiazolin-3-one 1,1-dioxide [81-07-2] $C_7H_5NO_3S$ (183.18).

Preparation—Toluene is reacted with chlorosulfonic acid to form o-toluenesulfonyl chloride, which is converted to the sulfonamide with ammonia. The methyl group then is oxidized with dichromate yielding o-sulfamoylbenzoic acid which, when heated, forms the cyclic imide.

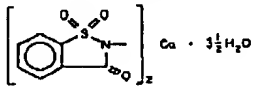
Description—White crystals or a white crystalline powder; odorless or has a faint aromatic odor; in dilute solution it is intensely sweet; solutions are acid to litmus; melts between 226 to 230°.

Solubility—1 g in 290 mL of water, 31 mL of alcohol or 25 mL of boiling water; slightly soluble in chloroform or ether; readily dissolved by dilute solution of ammonia, solutions of alkali hydroxides or solutions of alkali carbonates with the evolution of CO_2.

Uses—A sweetening agent in *Aromatic Cascara Sagrada Fluidextract* and highly alcoholic preparations. It is an intensely sweet substance. A 60-mg portion is equivalent in sweetening power to approximately 30 g of sucrose. It is used as a *sweetening agent* in vehicles, canned foods, beverages and in diets for diabetics to replace the sucrose. The relative sweetening power of saccharin is increased by dilution.

Saccharin Calcium

1,2-Benzisothiazol-3(2*H*)-one, 1,1-dioxide, calcium salt, hydrate (2:7)
Calcium o-Benzosulfimide



1,2-Benzisothiazolin-3-one 1,1-dioxide calcium salt hydrate (2:7) [6381-91-5] $C_{14}H_8CaN_2O_6S_2.3\frac{1}{2}H_2O$ (467.48); *anhydrous* [6485-34-3] (404.43).

Preparation—Saccharin is reacted with a semimolar quantity of calcium hydroxide in aqueous medium and the resulting solution is concentrated to crystallization.

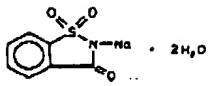
Description—White crystals or a white, crystalline powder; odorless or has a faint aromatic odor; and an intensely sweet taste even in dilute solutions; in dilute solution it is about 300 times as sweet as sucrose.

Solubility—1 g in 2.6 mL of water or 4.7 mL of alcohol.

Uses and Dose—See *Saccharin.*

Saccharin Sodium

1,2-Benzisothiazol-3(2*H*)-one, *1,1-dioxide, sodium salt, dihydrate; Soluble Saccharin; Soluble Gluside; Sodium o-Benzosulfimide*



1,2-Benzisothiazolin-3-one 1,1-dioxide sodium salt dihydrate [6155-57-3] $C_7H_4NNaO_3S.2H_2O$ (241.19); *anhydrous* [128-44-9] (205.16).

Preparation—Saccharin is dissolved in an equimolar quantity of aqueous sodium hydroxide and the solution is concentrated to crystallization.

Description—White crystals or a white crystalline powder; odorless or has a faint aromatic odor and an intensely sweet taste even in dilute solutions; in dilute solution it is about 300 times as sweet as sucrose; when in powdered form it usually contains about ½ the theoretical amount of water of hydration due to efflorescence.

Solubility—1 g in 1.5 mL of water or 50 mL of alcohol.

Uses—Same as *Saccharin* but has the advantage of being more soluble in neutral aqueous solutions.

Application—15 to 60 mg as necessary.

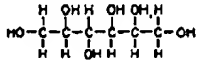
Dosage Form—Tablets: 15, 30 and 60 mg.

Sarsaparilla Syrup, Compound—RPS-13, page 445.

Sherry Wine—page RPS-15, page 1240.

Sorbitol

Sionin; Sorbit; D-Sorbitol; D-Glucitol Sorbo (*Atlas*)



D-Glucitol [50-70-4] $C_6H_{14}O_6$ (182.17); it may contain small amounts of other polyhydric alcohols.

Preparation—Commercially by reduction (hydrogenation) of certain sugars, such as glucose.

Description—White, hygroscopic powder, granules or flakes, having a sweet taste; the usual form melts about 96°.

Solubility—1 g in about 0.45 mL of water; slightly soluble in alcohol, methanol or acetic acid.

Uses—An *osmotic diuretic* given intravenously in 50% (*w/v*) solution to diminish edema, lower cerebrospinal pressure or reduce intraocular pressure in glaucoma. It also is used as a laxative, sweetener, humectant, plasticizer and, in 70% (*w/w*) solution, as a vehicle.

Dose—50 to 100 mL of a 50% solution; *laxative, oral*, 30 to 50 g.

Sorbitol Solution is a water solution containing, in each 100 g, 69–71 g of total solids consisting essentially of D-sorbitol and a small amount of mannitol and other isomeric polyhydric alcohols. The content of D-sorbitol [$C_6H_8(OH)_6$] in each 100 g is not less than 64 g. *Description:* Clear, colorless, syrupy liquid, having a sweet taste and no characteristic odor; neutral to litmus; specific gravity not less than 1.285; refractive index at 20° 1.455 to 1.465. *Uses:* It is not to be injected. It has been used as a replacement for propylene glycol and glycerin.

Spearmint

Spearmint Leaves; Spearmint Herb; Mint

The dried leaf and flowering top of *Mentha spicata* Linné (*Mentha viridis* Linné) (Common Spearmint) or of *Mentha cardiaca* Gerard ex Baker (Scotch Spearmint) (Fam *Labiatae*).

Fresh spearmint is used in preparing mint sauce and also the well-known mint julep. The volatile oil is the only constituent of importance in this plant; the yield is from ½ to 1%.

Uses—A flavoring agent.

Spearmint Oil is the volatile oil distilled with steam from the fresh over-ground parts of the flowering plant of *Mentha spicata* or of *Mentha cardiaca;* contains not less than 55%, by volume, of $C_{10}H_{14}O$ (carvone = 150.22). The chief odoriferous constituent is the ketone *l-carvone*. American oil also contains *dihydrocarveol acetate* [$CH_3COOC_{10}H_{17}$], *l-limonene* [$C_{10}H_{16}$], a small amount of *phellandrene* [$C_{10}H_{16}$] and traces of *esters of valeric* and *caproic acids*. Colorless, yellow or greenish yellow liquid, having the characteristic odor and taste of spearmint; specific gravity 0.917 to 0.934; soluble in 1 volume of 80% alcohol, but upon further dilution may become turbid. *Uses:* Primarily as a flavoring agent. It also has been used as a *carminative* in doses of 0.1 mL.

Sucrose

α-D-Glucopyranoside, β-D-fructofuranosyl-, Sugar; Cane Sugar; Beet Sugar

Sucrose [57-50-1] $C_{12}H_{22}O_{11}$ (342.30); a sugar obtained from *Saccharum officinarum* Linné (Fam *Gramineae*), *Beta vulgaris* Linné (Fam *Chenopodiaceae*), and other sources. It contains no added substances.

For the structural formula, see page 382.

Preparation—Commercially from the sugar cane, beet root and sorghum. Originally, sugar cane was the only source, but at present the root of *Beta vulgaris* is used largely in Europe, and to an increasing degree in this country, for making sucrose.

The sugar cane is crushed and the juice amounting to about 80% is expressed with roller mills. The juice after "defecation" with lime and removal of excess of lime by carbonic acid gas, is run into vacuum pans for concentration and the saccharine juice is evaporated in this until it begins to crystallize. After the crystallization is complete, the warm mixture of crystals and syrup is run into centrifuges, in which the crystals of raw sugar are drained and dried. The syrup resulting as a by-product from raw sugar is known as *molasses*. Raw beet sugar is made by a similar process, but is more troublesome to purify than that made from sugar cane.

The refined sugar from either raw cane or beet sugar is prepared by dissolving the raw sugar in water, clarifying, filtering and, finally, decolorizing the solution by passing it through bone-black filters. The water-white solution finally is evaporated under reduced pressure to the crystallizing point and then forced to crystallize in small granules which are collected and drained in a centrifuge.

Description—Colorless or white crystals, crystalline masses or blocks, or a white, crystalline powder; odorless; sweet taste; stable in air; solutions neutral to litmus; melts with decomposition from 160 to 185°; specific gravity of about 1.57; specific rotation at 20° not less than +65.9°; unlike the other official sugars (dextrose, fructose and lactose), it does not reduce Fehling's solution even in hot solutions; also differs from these sugars in that it is darkened and charred by sulfuric acid in the cold; fermentable and, in dilute aqueous solutions, it ferments into alcohol and eventually acetic acid.

Sucrose is hydrolyzed by dilute mineral acids, slowly in the cold, and rapidly on heating into one molecule each of dextrose or levulose. This process is known technically as "inversion" and the product is referred to as "invert sugar;" the term inversion being derived from the change, through the hydrolysis, in the optical rotation from dextro of the sucrose to levo of the hydrolyzed product. The enzyme *invertase* also hydrolyzes sucrose.

Solubility—1 g in 0.5 mL of water, 170 mL of alcohol or in slightly more than 0.2 mL of boiling water; insoluble in chloroform or ether.

Uses—Principally as a pharmaceutical necessity for making syrups and lozenges. It gives viscosity and consistency to fluids.

Intravenous administration of hypertonic solutions has been employed chiefly to initiate *osmotic diuresis*. Such a procedure is not completely safe and renal tubular damage may result, particularly in patients with existing renal pathology. Safer and more effective diuretics are available.

Compressible Sugar

Sucrose that may contain some starch, malto-dextrin or invert sugar; contains 95.0 to 98.0% of sucrose.

Description—White, crystalline, odorless powder; sweet taste; stable in air.

Solubility—The sucrose portion is very soluble in water.

Uses—A *pharmaceutic aid* as a *tableting excipient* and *sweetening agent*. See also *Sucrose*.

Confectioner's Sugar

Sucrose ground together with corn starch to a fine powder; contains 95.0 to 97.0% of sucrose.

Description—Fine, white, odorless powder; sweet taste; stable in air; specific rotation not less than +62.6°.

Solubility—The sucrose portion is soluble in cold water; this is entirely soluble in boiling water.

Uses—A *pharmaceutic aid* as a *tableting excipient* and *sweetening agent*. See also *Sucrose*.

Syrup—page 1302.

Tolu Balsam

Tolu

A balsam obtained from *Myroxylon balsamum* (Linné) Harms (Fam *Leguminosae*).

Constituents—Up to 80% *resin*, about 7% *volatile oil*, 12 to 15% free *cinnamic acid*, 2 to 8% benzoic acid and 0.05% *vanillin*. The volatile oil is composed chiefly of *benzyl benzoate* and *benzyl cinnamate*, *ethyl benzoate*, *ethyl cinnamate*, a terpene called *tolene* (possibly identical with *phellandrene*) and the sesquiterpene alcohol *farnesol* also have been reported to be present.

Description—Brown or yellowish brown, plastic solid; transparent in thin layers and brittle when old, dried or exposed to cold temperatures; pleasant, aromatic odor resembling that of vanilla and a mild, aromatic taste.

Solubility—Nearly insoluble in water or in solvent hexane; soluble in alcohol, chloroform or ether, sometimes with slight residue or turbidity.

Uses—A *vehicle*, *flavoring agent* and stimulating *expectorant* as a syrup. It is also an ingredient of *Compound Benzoin Tincture* (page 760).

Tolu Balsam Syrup [Syrup of Tolu; Tolu Syrup]—*Preparation:* Add tolu balsam tincture (50 mL, all at once) to magnesium carbonate (10 g) and sucrose (60 g) in a mortar, and mix intimately. Gradually add purified water (430 mL) with trituration, and filter. Dissolve the remainder of sucrose (760 g) in the clear filtrate with gentle heating, strain the syrup while warm and add purified water (qs) through the strainer to make the product measure 1000 mL. Mix thoroughly. *Note:* May be made also in the following manner: Place the remaining sucrose (760 g) in a suitable percolator, the neck of which nearly is filled with loosely packed cotton, moistened after packing with a few drops of water. Pour the filtrate, obtained as directed in the formula above, upon the sucrose, and regulate the outflow to a steady drip of percolate. When all of the liquid has run through, return portions of the percolate, if necessary, to dissolve all of the sucrose. Then pass enough purified water through the cotton to make the product measure 1000 mL. Mix thoroughly. *Alcohol Content:* 3 to 5%. *Uses:* Chiefly for its agreeable *flavor* in cough syrups. *Dose:* 10 mL.

Tolu Balsam Tincture [Tolu Tincture]—*Preparation:* With tolu balsam (200 g), prepare a tincture by Process M (page 1543), using alcohol as the menstruum. *Alcohol Content:* 77 to 83%. *Uses:* A balsamic preparation employed as an addition to expectorant mixtures; also used in the preparation of *Tolu Balsam Syrup*. *Dose:* 2 mL.

Vanilla

Vanilla Bean

The cured, full-grown, unripe fruit of *Vanilla planifolia* Andrews, often known in commerce as Mexican or Bourbon Vanilla, or of *Vanilla tahitensis* J W Moore, known in commerce as Tahiti Vanilla (Fam *Orchidaceae*); yields not less than 12% of anhydrous extractive soluble in diluted alcohol.

Constituents—Contains a trace of a volatile oil, fixed oil, 4% resin, sugar, *vanillic acid* and about 2.5% *vanillin* (see below). This highest grade of vanilla comes from Madagascar; considerable quantities of the drug also are produced in Mexico.

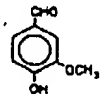
Uses—A flavor.

Note—Do not use if it has become brittle.

Vanilla Tincture [Extract of Vanilla]—*Preparation:* Add water (200 mL) to comminuted vanilla (cut into small pieces, 100 g) in a suitable covered container, and macerate during 12 hr, preferably in a warm place. Add alcohol (200 mL) to the mixture of vanilla and water, mix well and macerate about 3 days. Transfer the mixture to a percolator containing sucrose (in coarse granules, 200 g), and drain; then pack the drug firmly, and percolate slowly, using diluted alcohol (qs) as the menstruum. If the percolator is packed with an evenly distributed mixture of the comminuted vanilla, sucrose and clean, dry sand, the increased surface area permits more efficient percolation. This tincture is unusual in that it is the only official one in which sucrose is specified as an ingredient. *Alcohol Content:* 38 to 42%. *Uses:* A *flavoring agent*. See *Flavors*, page 1290.

Vanillin

Benzaldehyde, 4-hydroxy-3-methoxy-.



4-Hydroxy-3-methoxybenzaldehyde [121-33-5] $C_8H_8O_3$ (152.15).

Preparation—From vanilla, which contains 2 to 3%. It also is found in many other substances, including tissues of certain plants, crude beet sugar, asparagus and even asafetida. Commercially, it is made synthetically. While chemically identical with the product obtained from the "vanilla bean," "flavoring preparations" made from it never equal in flavor the preparation in which vanilla alone is used because vanilla contains other odorous products. It is synthesized by oxidation processes from either coniferin or eugenol, by treating guaiacol with chloroform in the presence of an alkali, and by other methods.

Description—Fine, white to slightly yellow crystals, usually needle-like having an odor and taste suggestive of vanilla; affected by light; solutions are acid to litmus; melts from 81 to 83°.

Solubility—1 g in about 100 mL of water, about 20 mL of glycerin or 20 mL of water at 80°; freely soluble in alcohol, chloroform, ether or solutions of the fixed alkali hydroxides.

Incompatibilities—Combines with *glycerin*, forming a compound which is almost insoluble in alcohol. It is decomposed by *alkalies* and is oxidized slowly by the *air*.

Uses—Only as a *flavor*. Solutions of it sometimes are sold as a synthetic substitute for vanilla for flavoring foods but it is inferior in flavor to the real vanilla extract.

Water—page 1300.

Water, Purified—page 1301.

Wild Cherry Syrup—page 1302.

Other Flavoring Agents

Anise NF IX [Anise Seed; European Aniseed; Sweet Cumin]—The dried ripe fruit of *Pimpinella anisum* Linné. It contains about 1.75% of volatile oil. *Uses:* A flavor and carminative.

Ceylon Cinnamon—The dried inner bark of the shoots of coppiced trees of *Cinnamomum zeylanicum* Nees (Fam *Lauraceae*); contains, in each 100 g, not less than 0.5 mL volatile oil. *Uses:* A *carminative* and *flavor*.

Clove—The dried flower-bud of *Eugenia caryophyllus* (Sprengel) Bullock et Harrison (Fam *Myrtaceae*). It contains, in each 100 g, not less than 16 mL of clove oil. *Uses:* An *aromatic* in doses of 0.25 g and as a condiment in foods.

Coriander—The dried ripe fruit of *Coriandrum sativum* Linné (Fam *Umbelliferae*); yields not less than 0.25 mL volatile coriander oil/100 g. *Uses:* Seldom used alone, but sometimes is combined with other agents, chiefly as a *flavor*. It also is used as a condiment and flavor in cooking.

Eucalyptol [Cineol; Cajeputol; $C_{10}H_{18}O$ (154.25)]— Obtained from eucalyptus oil and from other sources. Colorless liquid, having a characteristic, aromatic, distinctly camphoraceous odor and a pungent, cooling, spicy taste. 1 volume is soluble in 5 volumes of 60% alcohol; miscible with alcohol, chloroform, ether, glacial acetic acid or fixed or volatile oils; insoluble in water. *Uses:* Primarily as a *flavoring agent*. Locally it is employed for its *antiseptic* effect in inflammations of the nose and throat and in certain skin diseases. It sometimes is used by inhalation in bronchitis.

Fennel [Fennel Seed]—The dried ripe fruit of cultivated varieties of *Foeniculum vulgare* Miller (Fam *Umbelliferae*); contains 4 to 6% of an oxygenated volatile oil and 10% of a fixed oil. *Uses:* A *flavor* and *carminative*.

Ginger NF [Zingiber]—The dried rhizome of *Zingiber officinale* Roscoe (Fam *Zingiberaceae*), known in commerce as Jamaica Ginger, African Ginger and Cochin Ginger. The outer cortical layers often are removed either partially or completely. *Constituents:* A pungent substance, *gingerol*; volatile oil (Jamaica Ginger, about 1%; African Ginger, 2 to 3%), containing the terpenes *d-camphene* and *β-phellandrene* and the sesquiterpene *zingiberene*; *citral cineol* and *borneol*. *Uses:* A *flavoring agent*. It formerly was employed in a dose of 600 mg as an intestinal stimulant and carminative in colic and in diarrhea.

Ginger Oleoresin—Yields 18 to 35 mL of volatile ginger oil/100 g of oleoresin. *Preparation:* Extract the oleoresin from ginger, in moderately coarse powder, by percolation, using either acetone, alcohol or ether as the menstruum.

Glycyrrhiza Extract [Licorice Root Extract; Licorice]—An extract prepared from the rhizome and roots of species of *Glycyrrhiza* Tournefort ex Linné (Fam *Leguminosae*). *Description:* Brown powder or in flattened, cylindrical rolls or in masses; the rolls or masses have a glossy

black color externally, and a brittle, sharp, smooth, conchoidal fracture; the extract has a characteristic and sweet taste which is not more than very slightly acrid. *Uses:* A *flavoring agent.*

Lavender [Lavandula]—The flowers of *Lavandula spica* (*Lavandula officinalis* or *Lavandula vera*); contains a volatile oil with the principal constituent *l*-linalyl acetate. *Uses:* A *perfume.*

Lemon Peel USP XV, BP [Fresh Lemon Peel]—The outer yellow rind of the fresh ripe fruit of *Citrus limon* (Linné) Burmann filius (Fam *Rutaceae*); contains a volatile oil and hesperidin. *Uses:* A *flavor.*

Lemon Tincture USP XVIII [Lemon Peel Tincture]—*Preparation:* From lemon peel, which is the outer yellow rind of the fresh, ripe fruit of *Citrus limon* (Linné) Burmann filius (Fam *Rutaceae*), by *Process M* (page 1543), 500 g of the peel being macerated in 900 mL alcohol and the preparation being completed with alcohol to make the product measure 1000 mL. Use talc as the filtering medium. The white portion of the rind must not be used, as the proportion of oil, which is found only in the yellow rind, is reduced and the bitter principle, hesperidin, introduced. *Alcohol Content:* 62 to 72%. *Uses:* A flavor, its fineness of flavor being assured as it comes from the fresh fruit, and being an alcoholic solution it is more stable than the oil.

Myrcia Oil [Bay Oil; Oil of Bay]—The volatile oil distilled from leaves of *Pimenta racemosa* (Miller) J W Moore (Fam *Myrtaceae*); contains the phenolic compounds eugenol and chavicol. *Uses:* In the preparation of bay rum as a *perfume.*

Orange Oil, Bitter—The volatile oil obtained by expression from the fresh peel of the fruit of *Citrus aurantium* Linné (Fam *Rutaceae*); contains primarily *d*-limonene. Pale yellow liquid with a characteristic, aromatic odor of the Seville orange: if it has a terebinthinate odor, it should not be dispensed; refractive index 1.4725 to 1.4755 at 20°. It differs little from *Orange Oil* (page 1296) except for the botanical source. Miscible with anhydrous alcohol and with about 4 volumes alcohol. *Uses:* A *flavor.*

Orange Peel, Bitter [Bitter Orange; Curacao Orange Peel; Bigarade Orange]—The dried rind of the unripe but fully grown fruit of *Citrus aurantium* Linné (Fam *Rutaceae*). *Constituents:* The inner part of the peel from the bitter orange contains a volatile oil and the glycoside *hesperidin* ($C_{28}H_{34}O_{15}$). This, upon hydrolysis in the presence of H_2SO_4, yields *hesperetin* ($C_{16}H_{14}O_6$), *rhamnose* ($C_6H_{12}O_5$), and D-glucose ($C_6H_{12}O_6$). *Uses:* A *flavoring agent.* It has been used as a bitter.

Orange Peel, Sweet USP XV—The fresh, outer rind of the non-artificially colored, ripe fruit of *Citrus sinensis* (Linné) Osbeck (Fam *Rutaceae*); the white, inner portion of the rind is to be excluded. Contains a volatile oil but no hesperidin, since the glycoside occurs in the white portion of the rind. *Uses:* A *flavor.*

Orris [Orris Root; Iris; Florentine Orris]—The peeled and dried rhizome of *Iris germanica* Linné, including its variety *florentina* Dykes (*Iris florentina* Linné), or of *Iris pallida* Lamarck (Fam *Iridaceae*); contains about 0.1 to 0.2% of a volatile oil (orris butter), myristic acid and the ketone irone; irone provides the fragrant odor of orris. *Uses:* A *perfume.*

Pimenta Oil [Pimento Oil; Allspice Oil]—The volatile oil distilled from the fruit of *Pimenta officinalis* Lindley (Fam *Myrtaceae*). *Uses:* A *carminative* and *stimulant* and also as a *condiment* in foods.

Rosemary Oil—The volatile oil distilled with steam from the fresh flowering tops of *Rosmarinus officinalis* Linné (Fam *Labiatae*); yields not less than 1.5% of esters calculated as bornyl acetate ($C_{12}H_{20}O_2$), and not less than 8% of total borneol ($C_{10}H_{18}O$), free and as esters. *Constituents:* The amount of esters, calculated as bornyl acetate, and of total borneol, respectively, varies somewhat with its geographic source. Cineol is present to the extent of about 19–25%, depending on the source. The terpenes *d*- and *l*-*α*-*pinene*, *dipentene* and *camphene*, and the ketone *camphor* also occur in this oil. *Description:* Colorless or pale yellow liquid, having the characteristic odor of rosemary, and a warm, camphoraceous taste; specific gravity 0.894 to 0.912. Soluble in 1 volume of 90% alcohol, by volume, but upon further dilution may become turbid. *Uses:* A *flavor* and *perfume*, chiefly, in rubefacient liniments such as *Camphor and Soap Liniment.*

Sassafras—The dried bark of the root of *Sassafras albidum* (Nuttall) Nees (Fam *Lauraceae*). *Uses:* Principally because of its high content of volatile oil which serves to disguise the taste of disagreeable substances. An infusion (*sassafras tea*) formerly was used extensively as a home remedy, particularly in the southern states.

Sassafras Oil—The volatile oil distilled with steam from *Sassafras.* *Uses:* A *flavor* by confectioners, particularly in hard candies. Either the oil or safrol is used as a *preservative* in mucilage and library paste, being far superior to methyl salicylate for this purpose. Since the oil is *antiseptic*, it sometimes is employed in conjunction with other agents for local application in diseases of the nose and throat; safrol also is used in this way.

Wild Cherry [Wild Black Cherry Bark]—The carefully dried stem bark of *Prunus serotina* Ehrhart (Fam *Rosaceae*), free of borke and preferably having been collected in autumn. *Constituents:* A glucoside of *d*-*mandelonitrile* ($C_6H_5.CHOH.CN$) known as *prunasin* (page 385), the enzyme *emulsin*, tannin, a bitter principle, starch, resin, etc. In the BP and the English literature this drug has been termed "Virginian Prune"—a literal but incorrect translation of the older botanical name, *Prunus virginiana.* *Uses:* A *flavoring agent*, especially in cough preparations. It is an ingredient in *Wild Cherry Syrup.* As with bitter almond, contact with water, in the presence of emulsin, results in the production of benzaldehyde and HCN. All preparations of wild cherry should be made without heat in order to avoid destruction of the enzyme which is responsible for the production of the free active principles.

Diluting Agents

Diluting agents (vehicles or carriers) are indifferent substances which are used as solvents for active medicinals. They are of primary importance for diluting and flavoring drugs which are intended for oral administration, but a few such agents are designed specifically for diluting parenteral injections. The latter group is considered separately.

The expert selection of diluting agents has been an important factor in popularizing the "specialties" of manufacturing pharmacists. Since a large selection of diluting agents is available in a choice of colors and flavors, the prescriber has an opportunity to make his own prescriptions more acceptable to the patient. The best diluting agent is usually the best solvent for the drug. Water-soluble substances, for example, should be flavored and diluted with an aqueous agent and alcohol-soluble drugs with an alcoholic vehicle. Thus, the diluting agents presented herein are divided into three groups on the basis of their physical properties: aqueous, hydroalcoholic and alcoholic.

Aqueous Diluting Agents

Aqueous diluting agents include aromatic waters, syrups and mucilages. Aromatic waters are used as diluting agents for water-soluble substances and salts, but cannot mask the taste of very disagreeable drugs. Some of the more common flavored aqueous agents and the official forms of water are listed below.

Orange Flower Water

Stronger Orange Flower Water; Triple Orange Flower Water

A saturated solution of the odoriferous principles of the flowers of *Citrus aurantium* Linné (Fam. *Rutaceae*), prepared by distilling the fresh flowers with water and separating the excess volatile oil from the clear, water portion of the distillate.

Description—Should be nearly colorless, clear or only faintly opalescent; the odor should be that of the orange blossoms; it must be free from empyreuma, mustiness and fungoid growths.

Uses—A *vehicle flavor* and *perfume* in syrups, elixirs and solutions.

Peppermint Water

A clear, saturated solution of peppermint oil in purified water, prepared by one of the processes described under *Aromatic Waters* (page 1522).

Uses—A *carminative* and *flavored vehicle.*

Dose—15 mL.

Tolu Balsam Syrup—page 1299.

Water

Water [7732-18-5] H_2O (18.02).